# The Place for ACE Inhibitors

Three articles appear in this issue of *Journal of General Internal Medicine* that provide important information regarding the value and use of angiotensin-converting enzyme (ACE) inhibitors.[1–3]

The observational cohort study by Rochon et al. demonstrates improvement in clinical outcomes in elderly patients with heart failure who were treated with ACE inhibitors.[1] This study reinforces and extends the known benefit of ACE inhibitors for congestive heart failure, in this case documenting the value of the drugs in patients somewhat older (mean age 79) than those studied in most earlier clinical trials. The study's conclusion of a causal relationship between the use of ACE inhibitors and improved outcome is strengthened by the dose-response relationship shown in their Table 3.[4]

Besides the study limitations nicely summarized by the authors, there may be concern over possible confounding of the ACE inhibitor-outcome relationship by beta-blocker use; there is an apparent increase in beta-blocker use with increasing dose of ACE inhibitor, as shown in their Table 2. One also wonders whether the survival benefit of higher ACE inhibitor dose is actually related to healthier subjects not otherwise identifiable through demographic features who could tolerate the higher dose of ACE inhibitor (and more frequent co-treatment with beta-blockers). And the authors' conclusion about the value of starting ACE inhibitors at low doses and increasing over time to achieve high doses is a reasonable conclusion, but they did not assess the outcome of such a strategy in their study. In fact, patients managed with increasing doses in their study would have been censored when the dose was increased. Despite the limitations, I believe that this is a strong study and that the conclusions are valid.

For years, we have known of the benefit of low-dose treatment with ACE inhibitors to prevent or delay diabetic nephropathy.[5–8] The inclusion of ACE inhibitor therapy is an element of a combined aggressive approach shown to be effective in significantly reducing cardiovascular mortality and nephropathy in type 2 diabetes.[9] Such consistent and convincing data on the value of these agents have resulted in widespread endorsement of their use in these patients. But, as Rosen et al. show in their article, use remains suboptimal.[2] Perhaps the good news in their study is that 1) there were no significant ethnic discrepancies in the overall rate of use of these medications, and 2) physician prescribing of ACE inhibitors for diabetics may actually be improving over time, which is consistent with other observations,[10] though the generalizability of this observation is uncertain.

Morimoto et al. integrated clinical data regarding the class-specific adverse event of cough as a response to ACE inhibitors.[3] They give relative weights to various known associations with ACE inhibitor-induced cough, and help predict the likelihood that this adverse event will occur or recur if an ACE inhibitor is administered to a patient. Yet it seems unlikely that clinicians will withhold these important and beneficial medications from an individual patient without at least a therapeutic trial, with the possible exception of those who have previously developed ACE inhibitor-induced cough. The angiotensin receptor blockers (ARBs) are reasonable alternatives for patients who do develop ACE inhibitor-induced cough, but they have somewhat higher wholesale costs, especially compared to generic ACE inhibitors.[11]

ACE inhibitors commonly cause mild renal dysfunction as the desired result of reducing intraglomerular pressure, thereby preventing damage if hypertension coexists with diabetes. A slight rise in serum creatinine is to be expected and is acceptable after starting an ACE inhibitor. If the serum creatinine rises more than 30% above baseline or progressively increases over time, the clinician should promptly discontinue the ACE inhibitor and consider renovascular disease or other conditions known to enhance ACE inhibitor nephrotoxicity.[12]

Perhaps part of the problem with incorrect or insufficient dosing of ACE inhibitors is that these agents are used for three different indications, and the therapeutic approach for each indication is different. The nephroprotection of ACE inhibitors in diabetes can be afforded with low doses, and no titration is necessary in the absence of concomitant hypertension or congestive heart failure. To treat hypertension, the dose of drug should be titrated up or down depending on the individual's response to the current dose with respect to the target blood pressure. But in patients with congestive heart failure, both clinical trials and the results from Rochon et al. suggest that treating with ACE inhibitors at a high dose (either starting with a high dose or steadily increasing the dose to achieve a high dose) provides the greatest benefit over time. Even when the patient's symptoms and blood pressure are fine at low or medium doses, we should not be lulled into a false sense of security but should push on to the high dose, only to be dissuaded from this goal by true clinical intolerance.

How do we improve the delivery of this important treatment to our patients with diabetes, hypertension, or congestive heart failure? We, as the clinical leadership in academic medical centers and affiliated sites, need to be role models in the proper use of these medications and tireless in teaching these concepts. We can help to develop and/or employ practice guidelines, even though awareness and use of guidelines is often disappointing.[13] Even some computerized reminders do not seem to help implement proper treatment.[14] With the new Accreditation Council for Graduate Medical Education (ACGME) requirements (effective July 2003) that include quality assessment of clinical practice,[15] we can encourage our residents to do formal projects on the proper use of these drugs, much like Rosen et al. This type of practice review will highlight the problem and hopefully, over time, enhance conformity with best practices. We can try checklists for patients, which have

some benefits, but, unfortunately, some checklists do not include ACE inhibitor therapy to prevent kidney disease.[16,17] Even when providers remember to give patients prescriptions, compliance remains disappointing and difficult to improve. Patients' knowledge of their disease and its complications may not be enough to solve the problem; depressive symptoms may be important as a cause of noncompliance.[18]

In summary, ACE inhibitors are important drugs with great benefit to our patients. We should use them properly and instruct our students and residents to use them properly, according to indication:

> Diabetes alone—low dose is sufficient
> Hypertension—titrate according to individual response
> Congestive heart failure—PUSH TO HIGH DOSE, whenever possible

It is imperative to continue to work on strategies to more uniformly bring these life-prolonging drugs to our patients.

—**Brent G. Petty, MD**, *Division of Clinical Pharmacology and Division of General Internal Medicine, Department of Medicine, and Department of Pharmacology and Molecular Sciences, Johns Hopkins University School of Medicine, Baltimore, Md.*

## References

1. Rochon PA, Sykora K, Bronskill SE, et al. Use of angiotensin-converting enzyme inhibitor therapy and dose-related outcomes in older adults with new heart failure in the community. J Gen Intern Med. 2004;19:676–73.
2. Rosen AB, Karter AJ, Liu JY, Selby JV, Schneider EC. Use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in high-risk clinical and ethnic groups with diabetes. J Gen Intern Med. 2004;19:669–75.
3. Morimoto T, Gandhi TK, Fiskio JM, et al. Development and validation of a clinical prediction rule for angiotensin-coverting enzyme inhibitor-induced cough. J Gen Intern Med. 2004;19:684–91.
4. Newman TB, Browner WS, Hulley SB. Enhancing causal inference in observational studies. In: Hulley SB, Cummings SR, Browner WS, *et al.*, eds. Designing Clinical Research. Philadelphia, Pa: Lippincott Williams & Williams; 2001:125–38.
5. Mathiesen ER, Hommel E, Giese J, Parving HH. Efficacy of captopril in postponing nephropathy in normotensive insulin dependent diabetic patients with microalbuminuria. BMJ. 1991;303:81–7.
6. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting enzyme inhibitors on diabetic nephropathy. N Engl J Med. 1993;329:1456–62.
7. Viberti G, Mogensen CE, Groop LC, et al. Effect of captopril on progression to clinical proteinuria in patients with insulin-dependent diabetes mellitus and microalbuminuria. JAMA. 1994;271:275–9.
8. Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet. 2000;355:253–9.
9. Gaede P, Vedel P, Larsen N, et al. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med. 2003;348:383–93.
10. Scarsi KK, Bjornson DC. The use of ACE inhibitors as renoprotective agents in Medicaid patients with diabetes. Ann Pharmacother. 2000;34:1002–6.
11. Thompson Medical Economics. 2003 Drug Topics Red Book. Montvale, NJ: Thompson Medical Economics, 2003.
12. Palmer BF. Renal dysfunction complicating the treatment of hypertension. N Engl J Med. 2002;347:1256–61.
13. Switzer GE, Halm EA, Chang C-CH, et al. Physician awareness and self-reported use of local and national guidelines for community-acquired pneumonia. J Gen Intern Med. 2003;18:816–23.
14. Tierney WM, Overhage JM, Murray MD, et al. Effects of computerized guidelines for managing heart disease in primary care: a randomized, controlled trial. J Gen Intern Med. 2003;18:967–76.
15. Accreditation Council for Graduate Medical Education. Program Requirements for Residency Education in Internal Medicine. Program Requirements, Internal Medicine, section V.B.3. Available at: http://www.ACGME.org. Accessed May 7, 2004.
16. Chapin RB, Williams DC, Adair RF. Diabetes control improved when inner-city patients received graphic feedback about glycosylated hemoglobin levels. J Gen Intern Med. 2003;18:120–4.
17. Lafata JE, Baker AM, Divine GW, McCarthy BD, Xi H. The use of computerized birthday greeting reminders in the management of diabetes. J Gen Intern Med. 2002;17:521–30.
18. Wang PS, Bohn RL, Knight E, et al. Noncompliance with antihypertensive medications: the impact of depressive symptoms and psychosocial factors. J Gen Intern Med. 2002;17:504–11.